PULSE WAVE ANALYSIS USING TONE-ENTROPY ALGORITHM IN PEOPLE WITH AND WITHOUT FOOT COMPLAINTS IN A RURAL DIABETES SCREENING CLINIC

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ABSTRACT
Peripheral arterial disease (PAD) affects 10–25% of people over the age of 55. It contributes to foot amputation, morbidity and mortality. Accurate and early diagnosis can lessen this public health burden. A current clinical measure of PAD such as the ankle brachial pressure index (ABPI) has low sensitivity and specificity for asymptomatic disease and calcified arteries especially in the diabetic population. Therefore, a new non-invasive evaluation method for lower limb vascularization has been investigated. Four groups of patients: non-diabetics and diabetics with and without foot problems and attending a diabetes complication screening clinic had their posterior tibial pulse velocity recorded. The pulse wave was segmented and inter-peak distances from 16-minute recordings identified. The tone-entropy algorithm for assessing pulse beat interval variation was applied to the data. Tone differentiated between non-diabetic and diabetes group with good foot health as well as for poor foot health. Entropy similarly was related to the level of foot health. A significant difference (p<0.05) was found between good foot health and poor foot health in the non-diabetes group. ABPI identified no significant differences between the four groups. The results suggest that the tone-entropy is a useful adjunct for screening for neuropathic-related foot problems that may be a risk indicator for peripheral arterial disease.

KEY WORDS
Peripheral arterial disease, peripheral pulse interval analysis, diabetes, ankle brachial index.

1. Introduction
Within Australia, peripheral arterial disease (PAD) affects 10–25% of people over the age of 55 [1]. PAD is a major risk factor for the development of cardiovascular and cerebrovascular disease that can lead to myocardial infarction and death [2]. Several diagnostic methods exist for the detection of PAD. These include angiography, the Ankle Brachial Pressure Index (ABPI) and pulse palpation (PP) [3]. Angiography is the current gold standard for determining the presence of PAD. Angiography however, is both a costly and an invasive procedure [4].

Pulse Wave Analysis (PWA) relies on detecting changes in blood flow through the vessels and can be recorded using a transducer such as a Doppler ultrasound instrument. PWA can be used to record from calcified vessels as well as indicating asymptomatic disease [5]. PWA has been shown to be effective in the early screening for cardiovascular disease using the carotid and/or radial artery [6]. Diagnosis from the pulse wave morphology is possible. However no definitive diagnostic criteria exist. Criteria such as the number of wave peaks, being either one, two or three, flattening of waveform and complex waveforms have been reported. The first peak represents the blood flow velocity due to blood being expelled from the ventricle during systole. The second wave peak represents the reversal flow velocity of early diastole due to the elastic distension in the arteries. The third peak represents the forward flow velocity during late diastole due to the rebound of the arteries [7]. The multitude of pulse waves and their subtle differences make it often difficult to diagnose PAD accurately.

A previous study has shown that sympatho-vagal balance can be detected even in the time domain through the tone-entropy (T-E) [8]. Tone was verified to reflect
the sympatho-vagal balance by a pharmacological experiment where tone changed in value consistently in a heart rate recovery experiment after exercise where the parasympathetic division became predominant [8].

The Pulse wave signals inherently contain heart periods, and the displayed pulse waves arise from heart-beat-dependent volume changes in the terminal arterial bed. Therefore, it can be used to conduct traditional HRV analyses. Pulse to pulse variability i.e. pulse rate variability (PRV) can be calculated from peak to peak time intervals of pulse wave signals.

Therefore, the aim of this study was to elucidate any alterations of cardiac autonomic functions in patients in relation to PAD in diabetic patients and healthy well-matched controls by T-E analysis.

2. Method

This study was granted ethics approval from the Charles Sturt University Human Ethics Committee. Participants were recruited from the Diabetes Complication Screening Initiative at the School of Community Health, CSU.

2.1 Participants

Participants were divided into non-diabetes and a diabetes group that had no known co-morbidities such as previous or current pathology including kidney disease, stroke, cardiovascular, or diagnosed peripheral vascular disease with good foot health. Two more groups comprised a non-diabetic and a diabetes group with diverse foot complaints such as tingling, heat, cold or loss of sensation. The four groups were non-diabetic healthy foot (NDHF), diabetic healthy foot (DMHF), non-diabetic poor foot health (NDPH) and diabetic poor foot health (DMPH) groups. Additional exclusion criteria included the following; participants with skin allergies, smoking more than 5 cigarettes a day (vasoconstrictor) and consuming more than 2 alcoholic drinks per day (standard glasses) (vasodilator).

2.2 Ankle Brachial Index and Pulse Interval Variation

The ABPI was determined using a Doppler ultrasound with an 8MHz probe and sphygmomanometer after a ten-minute rest. The systolic blood BP was taken on both arms and both legs. The ABPI was calculated by dividing the ankle systolic pressure by the arm (brachial) systolic pressure on both the left and the right side [3]. The results were recorded for each limb. Pulse wave morphology was similarly recorded using an 8MHz Doppler probe for 16 minutes. Peak-to-Peak distance in milliseconds was recorded for analysis

2.3 Tone-Entropy Determination

The T-E algorithm was previously described in details in [8]. The acquired pulse wave peak intervals are transformed into percentage index (PI) time series:

\[ PI(n) = \frac{(H(n) - H(n+1))}{H(n)} \times 100 \] (1)

where \( H(n) \) is a heart period time series, and \( n \) a serial number of heart beats. The tone is defined as a first order moment (arithmetic average) of this PI time series as:

\[ \sum_n PI(n) / N \] (non-dimensional) \] (2)

where \( N \) is a total number of PI terms. The tone, which represents the balance between accelerations (PI > 0) and inhibitions (PI < 0) of the heart, represents the sympatho-vagal balance [14,17]. The entropy is defined on PI probability distribution by using Shannon’s formula:

\[ -\sum_n p(i) \log_2 p(i) \] (bit) \] (3)

where \( p(i) \) is a probability that PI(n) has a value in the range, \( iPI(n) < i + 1, i \) an integer. The entropy evaluates total acceleration–inhibition activities, or total heart period variations in a familiar unit of bit as described by [10], where autonomic control of heart rate was studied as an antagonistic interactive operation between acceleration and inhibition.

The T-E evaluation process is not influenced by the time period of data acquisition, nor the baseline heart rate. In addition, the T-E data processing has no signal deformation process such as filtering, window, or limiting process. A very important advantage is that there is no need to control respiration rate in the T-E method, allowing data to be obtained in a natural process [8].

2.4 Statistical Analysis

Significant differences between groups was determined using ANOVA (SPSS Version 17) followed by post hoc analysis. Significance level was set at \( p<0.05 \).

3. Results

We recorded age, waist circumference, and cholesterol in 47 participants from the diabetes complications screening clinic as well their blood pressure, ankle brachial pressure index (ABPI), tone and entropy (Table 1)
Table 1
Demographics for Participants

<table>
<thead>
<tr>
<th>NDHF</th>
<th>DMHF</th>
<th>NDPF</th>
<th>DMPF</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58.3±7</td>
<td>62±10</td>
<td>76±8</td>
<td>64±6</td>
<td>13.5</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>84.5±8</td>
<td>91±20</td>
<td>95±10</td>
<td>110±10</td>
<td>9.63</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119±12</td>
<td>133±20</td>
<td>131±16</td>
<td>141±10</td>
<td>5.28</td>
</tr>
</tbody>
</table>

ND-non-diabetic; DM-diabetic; HF-healthy foot; PF-poor foot health; Waist-waist circumference; SBP-systolic blood pressure.

Table 2 shows the results for left and right leg ABPI, left and right leg systolic blood pressure as well as the average ABPI. There were no differences between left and right leg ABPI within the non-diabetes and diabetes groups. Nor was there a significant difference for the average ABPI between groups and the mean values were within the normal limits (0.9 – 1.3). Systolic blood pressure measured at the ankle of both right and left leg was raised for both left and right leg in participants with poor foot health in the non-diabetes as well as diabetes groups. It is worth noting that one participant had an abnormal right ABPI value of 1.3 but average ABPI of 1.21.

Table 2
ANOVA results for ABPI between groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>NDHF</th>
<th>DMHF</th>
<th>NDPF</th>
<th>DMPF</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABPI</td>
<td>1.2±0.1</td>
<td>1.1±0.1</td>
<td>1.1±0.2</td>
<td>1.0±0.3</td>
<td>1.46</td>
<td>0.25</td>
</tr>
<tr>
<td>RABPI</td>
<td>1.2±0.1</td>
<td>1.1±0.1</td>
<td>1.1±0.2</td>
<td>1.1±0.3</td>
<td>1.91</td>
<td>0.15</td>
</tr>
<tr>
<td>LSBP (mmHg)</td>
<td>135±13</td>
<td>143±25</td>
<td>144±25</td>
<td>144±41</td>
<td>0.33</td>
<td>0.8</td>
</tr>
<tr>
<td>RSBP (mmHg)</td>
<td>138±14</td>
<td>136±16</td>
<td>146±20</td>
<td>150±50</td>
<td>0.63</td>
<td>0.6</td>
</tr>
<tr>
<td>ABPI average</td>
<td>1.2±0.1</td>
<td>1.1±0.1</td>
<td>1.1±0.2</td>
<td>1.1±0.3</td>
<td>2.24</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*ND-non-diabetic; DM-diabetic; HF-healthy foot; PF-poor foot health; L-left; R-right; ABPI-ankle brachial index; SBP systolic blood pressure.

Pulse waves were analyzed for this study and the ANOVA and post hoc results shown in Table 3.

Table 3
Post hoc results for the four groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Tone</th>
<th>Entropy</th>
<th>Tone post hoc</th>
<th>Entropy post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDHF*</td>
<td>-1.75±0.01</td>
<td>4.24±0.3</td>
<td>NDHF and DMHF</td>
<td>NDHF and DMHF</td>
</tr>
<tr>
<td>DMHF</td>
<td>-0.086±0.3</td>
<td>4.03±0.4</td>
<td>DMHF and NDPF</td>
<td>DMHF and DMPF</td>
</tr>
<tr>
<td>NDPF</td>
<td>-2.65±2.3</td>
<td>3.76±0.5</td>
<td>NDHF and DMHF</td>
<td>NDHF and DMHF</td>
</tr>
<tr>
<td>DMPF</td>
<td>-1.57±1.2</td>
<td>4.27±0.4</td>
<td>NDHF and DMHF</td>
<td>NDHF and DMHF</td>
</tr>
</tbody>
</table>

*ND-non-diabetic; DM-diabetic; HF-healthy foot; PF-poor foot health.
** significant difference between groups

Comparing the outcomes for the non-diabetes and diabetes group with good foot health indicates an increase in tone in the diabetes group and a decrease in entropy. Foot health has a discordant effect on tone and entropy. For good foot health, entropy decreases in the diabetes group but for poor foot health entropy is seen to increase. Significant differences (p=0.05) were only seen for non-diabetes versus diabetes groups having poor foot health and for the non-diabetes good foot health versus non-diabetes poor foot health groups (p=0.01).

Figure 1 and 2 illustrate individual data for tone and entropy in NDHF, DMHF, NDPF and DMPF groups. A clear tendency was noticed corresponding diabetes status and for tone in participants who reported healthy feet.
4. Discussion

Correct and early diagnosis of PAD is essential to prevent complications and morbidity [11]. Within Australia, PAD resulted in 25,432 hospital admissions in 2002/03, and accounted for 2,478 deaths in 2003 [12]. The current gold standards are Doppler ultrasound and ankle brachial pressure index (ABPI), with the latter most often used in clinical practice. The ABPI is often not determinable especially if people have skin abrasion, are on dialysis, have ulcers or calcified vessels. The ABPI tests were not significant for all group comparisons. ABPI is an indicator for peripheral vascular disease more generally related to atherosclerosis and an increase in ankle blood pressure. Normal values for ABPI range between 0.8 and 1.3. Therefore common foot complaints such as cold, burning, tingling or pain may have a different aetiology. A previous study on an association between neuropathic sensory symptoms and a clinical neurological examination was not significant [13]. Therefore a better screening test is required.

Using a Doppler ultrasound to record the pulse wave velocity of the posterior tibial artery behind the lateral malleolus, the pulse interval changes were measured over a 16-minute recording and analysed. Tone-entropy has been shown to be a sensitive test for identification of sympathetic and parasympathetic influence of heart rate and cardiac autonomic neuropathy [8, 14].

Tone increased in the diabetes group regardless of whether foot health was poor or not suggesting that changes in blood flow velocity and peripheral pulse interval are affected by pathophysiological changes associated with diabetes. Entropy decreased as expected in the diabetes group and good foot health. However for poor foot health entropy was increased in the diabetes group. This unexpected result can be due to the small number of participants per group or due to pathophysiological factors. As such changes in blood flow velocity in people with poor foot health may not be related to diabetes status or diabetes status plays a minor role. This is consistent with reports that cold, burning or tingling feet are common in the general population and increase with age [15]. Peripheral neuropathy with an increased sympathetic tone and/or metabolic imbalance other than diabetes may also affect the blood flow characteristics and the inter-pulse intervals. Thus tone and entropy differences may have been masked by the influence of aging since there was a significant difference between the four groups [16, 17].

The only pathophysiological significant result was found for a difference between non-diabetic good foot health and non-diabetic poor foot health, where entropy decreased. Tone increased in the poor foot health group but was not significant.

Our findings are of importance as they shed light on the pathophysiology of foot complaints traditionally difficult to classify and to treat. The results indicate that the pulse interval changes associated with foot health are explainable by the tone and entropy provided there is no abnormal foot sensation present. However when abnormal foot sensations are reported the no clear association to tone and entropy is apparent suggesting that a complex multifactorial aetiology is responsible for these symptoms. Tone and entropy provides a novel diagnostic tool that is sensitive to changes in foot sensation and therefore provides the basis for further research into the aetiology of peripheral arterial disease and its management.

5. Conclusion

Changes in tone and entropy can be used to study the effect of smoking, obesity, hypertension, and dislipidemia and the reduction in these risk factors. In addition earlier detection may decrease the need for more complex and risky interventions such as vascular surgery, and reduce the risk of cardiovascular or cerebrovascular disease.

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References


